Paper No. 28

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

_____

Ex parte SU-SUN WANG

_____

Appeal No. 1997-0094
Application No. 08/188,232[1]

_____

ON BRIEF

_____

Before WILLIAM F. SMITH, SPIEGEL, and MILLS, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

DECISION ON APPEAL

Appellant's request for a hearing has been vacated as unnecessary. 37 CFR § 1.194(c).[2]

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 4 and 7. Claims 2, 3, 5 and 6, which are the only other claims pending in this application, stand withdrawn from further consideration by the examiner.

---

[1] Application for patent filed January 28, 1994.

[2] See facsimile communication dated October 3, 2000 (Paper No. 27).

Claims 1 and 4 are illustrative:

1. A compound of the formula:

X-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Z (I)

wherein X is an acetyl or pyroglutamyl group and

Z is -NH_2,
-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-Pro-NH_2,
-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-Gly-NH_2, or
-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn

with the proviso that when X is a pyroglutamyl group, Z is -Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn, and when X is an acetyl group, Z is other than -Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn.

4. The compound of claim 1 wherein X is an acetyl group and Z is -Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-Gly-NH_2 (SEQ ID NO: 3).

The prior art references of record relied on by the examiner are:

Haritos et al. (Haritos), "Prothymosin α: Isolation and properties of the major immunoreactive form of thymosin α_1 in rat thymus," Proceedings of the National Academy of Sciences, USA, Vol. 81, pp. 1008-1011 (February 1984).

Zatz et al. (Zatz), "Thymosins, Lymphokines, and the Immunology of Aging," Gerontology, Vol. 31, pp. 263-277 (1985).

Abiko et al. (Abiko II), "Synthesis and Immunological Effect of Deacetyl-thymosin α_{11} on Low E-Rosette-Forming Cells of a Rheumatoid Arthritis Patient," Chemical & Pharmaceutical Bulletin, Vol. 22, No. 12, pp. 5419-5427 (December 1985).

Ishimura et al. (Ishimura), "Antigenic Specificity of a Rabbit Antiserum Raised Against the 15-28 Segment of Thymosin "$_1$," Molecular Immunology, Vol. 23, No. 7, pp. 701-707 (1986).

Abiko et al. (Abiko I), "Synthesis of an Immunologically Active Fragment Analog of Prothymosin " with Enhanced Enzymatic Stability," Chemical & Pharmaceutical Bulletin, Vol. 39, No. 3 pp. 752-756 (March 1991).

ISSUE

Claims 1, 4 and 7 stand rejected under 35 U.S.C. § 103 as being unpatentable over either Haritos or Abiko I in view of any one of Abiko II or Zatz or Ishimura.

We REVERSE.

Initially, we note that here the examiner required appellant "to elect a single disclosed specie [sic] of the polypeptide and indicate claim(s) reading thereon or draw claim(s) to the elected specie [sic]" (Paper No. 4, mailed March 29, 1994, p. 3). Appellant, in turn, elected "Group I, claims 1-7, and thymosin "$_1$-gly amide of Example 3, for examination on the merits. Claims 1, 4 and 7 are readable thereon." (Paper No. 6, filed April 20, 1994). Thus, the specific issue presented for review is whether the compound thymosin "$_1$-gly amide would have been obvious under 35 U.S.C. § 103 in view of the prior art references cited and relied on by the examiner. We discuss that single issue infra and we take no position respecting the patentability of the remaining non-elected species.

In reaching our decision in this appeal we have given careful consideration to the appellant's specification and claims and to the respective positions articulated by the appellant and the examiner. We make reference to the examiner's answer (Paper No. 17, mailed May 14, 1996) and to the examiner's supplemental answer (Paper No. 20, mailed October 15, 1996) for the examiner's reasoning in support of the rejection and to the appellant's brief (Paper No. 16, filed December 4, 1995), to the appellant's reply brief (Paper No. 19, filed July 12, 1996) and to the appellant's second reply brief (Paper No. 21, filed December 16, 1996) for the appellant's arguments thereagainst.

BACKGROUND

Prothymosin ", a native thymic polypeptide isolated from thymosin fraction 5, is the precursor from which a number of biologically active peptides, including thymosin $"_1$ and two related peptides, des-(25-28)-thymosin $"_1$ and thymosin $"_{11}$, are derived. Thymosin $"_1$ is defined by the first 28 amino acid residues of the N-terminal of prothymosin "; des-(25-28)-thymosin $"_1$ by the first 24 amino acid residues; and, thymosin $"_{11}$ by the sequence of thymosin $"_1$ plus seven additional residues at the COOH terminus. See Haritos, p. 1008, c. 1 and Zatz, Table I.

THE INVENTION

The claimed invention is the compound thymosin "$_1$ gly-amide, i.e., a peptide consisting of amino acid residues 1-29 of the NH_2-terminal sequence of prothymosin " wherein the glycine residue at position 29 is amidated.

OPINION

Haritos discloses the NH_2-terminal sequence of the . 112 amino acid residue polypeptide, prothymosin ", including the sequences for thymosin "$_1$ and amino acid residues 1-30 for thymosin "$_{11}$ (Fig. 6, p. 1011).

Abiko I discloses a 30 amino acid residue thymosin "$_{11}$ analog having a D-Arg in place of the arginine residue at position 30, which analog has increased resistance to inactivation by enzyme (exopeptidase) degradation (abstract; p. 752).

Abiko II discloses synthetic deacetyl-thymosin "$_{11}$ (Fig. 2, p. 5420) as approximately equal in potency to synthetic deacetyl-thymosin "$_1$ in increasing E-rosette-forming capacity in cases of rheumatoid arthritis (p. 5419; Fig. 2, p. 5420). Ishimura discloses four peptides amides derived from thymosin "$_1$, i.e., amino acid residue (20-28), (20-27), (20-26) and [Ala-27](20-28) amides (see Figure 2(a), p. 703, peptides 19-22). According to Ishimura, "the major immunoreactive site of the COOH-terminal half of thymosin "$_1$ is segment (21-28), with important contributions by

Glu-21, Glu-27 and Asn-28" (p. 705, c. 2). Immunoreactivity decreased by about 40-fold if either Asn-28 or its terminal OH group was replaced by $-NH_2$ and by about 500-fold if the COOH-terminal dipeptide Glu-Asn was replaced by $-NH_2$ or Glu-27 was replaced by Ala (p. 705, c. 1).

Zatz describes the amino acid sequences of "-thymosins, including thymosin $"_1$, des (25-28) $"_1$, $"_{11}$ and prothymosin " (Fig. 1), and of ß-thymosins (Fig. 2) (p. 265).

According to the examiner, it would have been obvious to delete "one amino acid residue from the known 1-30 peptide fragment especially since the peptide activity is known to reside in the N-terminus fragment of 1-28 residues", i.e., in thymosin $"_1$ (answer, p. 6).

First, we note that the examiner has incorrectly defined the 1-30 amino acid residue fragment as thymosin $"_{11}$ (see answer, p. 3, "thymosin $alpha_{11}$ (1-30)"). Thymosin $"_{11}$ is the peptide defined by residues 1-35 of the N-terminal of prothymosin ". Second, even assuming arguendo that it would have been obvious to add one more amino acid residue to thymosin $"_1$ or to shorten the 30 amino acid residue thymosin $"_{11}$ analog of Akibo I by one amino acid residue to obtain an active peptide, the examiner has not explained why one of ordinary skill in the art would have amidated the
C-terminal amino acid, Gly-29.

Akibo I uses the D-form of the C-terminal amino acid residue Arg-30 to impart resistance to enzymatic degradation while retaining biological activity. Akibo I does not disclose or suggest amidating the C-terminal Arg-30 in either D- or L-form. Haritos does not disclose or suggest amidation.

According to the examiner, "Ishimura is employed for the teaching of amidating the C-terminus of the thymosin alpha family" (answer, p. 8). However Ishimura suggests that amidating the C-terminus region of a thymosin "$_1$ fragment markedly decreases immunoreactivity (p. 705, c. 1). Indeed, appellant argues that "[a]s is known in the art, changes in the peptide which detrimentally affect binding to antibodies [i.e., immunoreactivity] are likely to similarly affect binding to receptors and thus affect bioactivity" (brief, p. 11). In response, the examiner calls appellant's argument "mere[ly] speculative without factual basis" (answer, p. 9) and argues that if any binding activity was present "even to a small extent, [it] would suffice the finding of obviousness" (supplemental answer, p. 3). We disagree.

Establishing a prima facie case of obviousness requires both some suggestion or motivation to modify the reference or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Here, the examiner has not established that one of ordinary skill in the art

would have had a reasonable expectation of success of obtaining an active thymosin peptide by amidating the C-terminal of a thymosin "$_1$ and/or thymosin "$_{11}$ analog given the factual basis for appellant's above argument, i.e., the markedly decreased immunoreactivity of the amidated peptides of Ishimura. In short, the examiner has not explained why one of ordinary skill in the art would have amidated Gly-29 as claimed.

The examiner further states that "Zatz discloses amidation of the thymosin family irrespective of whether the compound belongs to the alpha or beta thymosin group" (answer, p. 8). However, the examiner has not pointed out, and we do not find, where Zatz addresses the issue of how amidating the C-terminal of a thymosin peptide affects its biological activity. At best, Zatz merely suggests the existence of an amide composition for thymosin ß$_9$ (caption beneath Fig. 2, p. 265).[3]

Thus, we find the examiner has not carried her burden of establishing a prima facie case of obviousness and has relied on impermissible hindsight in making her determination of obviousness. In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Having concluded that the examiner has not established a prima facie case of obviousness, we do not reach the rebuttal evidence in the Raitzer

[3] According to Table I (p. 267), thymosin ß$_9$ per se has no reported biological activity.

Declaration discussed in appellant's brief (pp. 5-7 and 13), reply brief (p. 11) and second reply brief (p. 4).

The rejection is reversed.

CONCLUSION

To summarize, the decision of the examiner to reject claims 1, 4 and 7 under 35 U.S.C. § 103 as being unpatentable over either Haritos or Abiko I in view of any one of Abiko II or Zatz or Ishimura is reversed.

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	)
CAROL A. SPIEGEL Administrative Patent Judge	) BOARD OF PATENT) APPEALS) AND) INTERFERENCES
DEMETRA J. MILLS Administrative Patent Judge	)

ROTHWELL, FIGG, ERNST & KURZ
SUITE 701-E
555 13TH STREET, N.W.
WASHINGTON, DC 20004

CAS/jlb